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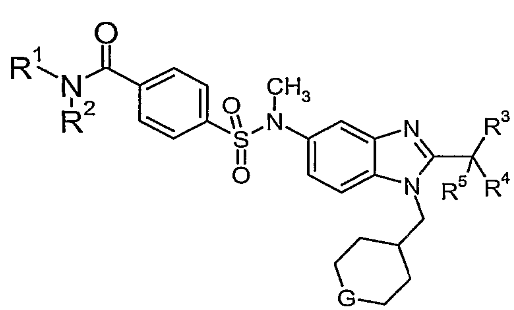
**(54) Title:** BENZIMIDAZOLE DERIVATIVES, COMPOSITIONS CONTAINING THEM, PREPARATION THEREOF AND USES THEREOF



I

**(57) Abstract:** Compounds of Formula I or pharmaceutically acceptable salts thereof wherein G, $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are as defined in the specification as well as salts and pharmaceutical compositions including the compounds are prepared. They are useful in therapy, in particular in the management of pain.

WO 2006/033628 A1

# BENZIMIDAZOLE DERIVATIVES, COMPOSITIONS CONTAINING THEM, PREPARATION THEREOF AND USES THEREOF

## BACKGROUND OF THE INVENTION

### 1. Field of the invention

The invention is related to therapeutic compounds, pharmaceutical compositions containing these compounds, manufacturing processes thereof and uses thereof. Particularly, the present invention is related to compounds that may be effective in treating pain, cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and/or cardiovascular disorders.

### 2. Discussion of Relevant Technology

Pain management has been studied for many years. It is known that cannabinoid receptor (e.g., $CB_1$ receptor, $CB_2$ receptor) ligands including agonists, antagonists and inverse agonists produce relief of pain in a variety of animal models by interacting with $CB_1$ and/or $CB_2$ receptors. Generally, $CB_1$ receptors are located predominately in the central nervous system, whereas $CB_2$ receptors are located primarily in the periphery and are primarily restricted to the cells and tissues derived from the immune system.

While $CB_1$ receptor agonists, such as $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) and anadamide, are useful in anti-nociception models in animals, they tend to exert undesired CNS side-effects, e.g., psychoactive side effects, the abuse potential, drug dependence and tolerance, etc. These undesired side effects are known to be mediated by the $CB_1$ receptors located in CNS. There are lines of evidence, however, suggesting that $CB_1$ agonists acting at peripheral sites or with limited CNS exposure can manage pain in humans or animals with much improved overall in vivo profile.

Therefore, there is a need for new $CB_1$ receptor ligands such as agonists that may be useful in managing pain or treating other related symptoms or diseases with reduced or minimal undesirable CNS side-effects.

## DESCRIPTION OF THE EMBODIMENTS

The present invention provides $CB_1$ receptor ligands which may be useful in treating pain and/or other related symptoms or diseases.

The term "$C_{m-n}$" or "$C_{m-n}$ group" used alone or as a prefix, refers to any group having m to n carbon atoms.

The term "alkyl" used alone or as a suffix or prefix, refers to a saturated monovalent straight or branched chain hydrocarbon radical comprising 1 to about 12 carbon atoms. Illustrative examples of alkyls include, but are not limited to, $C_{1-4}$alkyl groups, such as methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, butyl, isobutyl, t-butyl.

The term "cycloalkyl," used alone or as suffix or prefix, refers to a saturated monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms. Examples of cycloalkyls include, but are not limited to, $C_{3-7}$cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes. A cycloalkyl can be unsubstituted or substituted by one or two suitable substituents. Preferably, the cycloalkyl is a monocyclic ring or bicyclic ring.

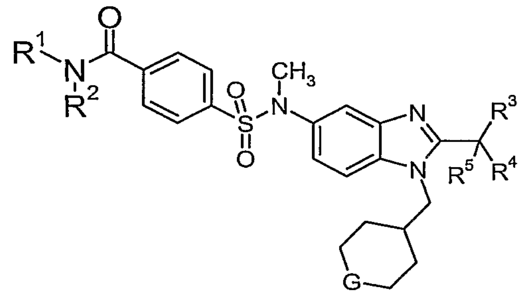
The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula –O-R, wherein R is an alkyl. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, and isobutoxy.

The term "heterocylcoalkyl" used alone or as a suffix or prefix, refers to a monocyclic or polycyclic ring comprising carbon and hydrogen atoms and at least one heteroatom, preferably, 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and having no unsaturation. Examples of heterocycloalkyl groups include pyrrolidinyl, pyrrolidino, piperidinyl, piperidino, piperazinyl, piperazino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, and pyranyl. A heterocycloalkyl group can be unsubstituted or substituted with one or two suitable substituents. Preferably, the heterocycloalkyl group is a monocyclic or bicyclic ring, more preferably, a monocyclic ring, wherein the ring comprises from 2 to 5 carbon atoms and from 1 to 3 heteroatoms, referred to herein as $C_{2-5}$heterocycloalkyl.

Halogen includes fluorine, chlorine, bromine and iodine.

"RT" or "rt" means room temperature.

In one aspect, an embodiment of the invention provides a compound of Formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



I

wherein

G is selected from –O-, -CHF-, and –$CF_2$-;

$R^1$ and $R^2$ are independently selected from –H, hydroxy, $C_{1-4}$alkyl, $C_{3-6}$cycloalkyl, $C_{1-4}$alkoxy-$C_{1-4}$alkyl, $C_{1-4}$alkoxy, and hydroxy-$C_{1-4}$alkyl; or $R^1$ and $R^2$ together with the nitrogen linked thereto form a $C_{2-5}$cycloheteroalkyl; and

$R^3$, $R^4$ and $R^5$ are independently selected from fluoro and methyl.

In another embodiment, the compounds may be those of formula I, wherein

G is selected from –O- and –$CF_2$-;

$R^1$ and $R^2$ are independently selected from –H, hydroxy, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, and hydroxy-$C_{1-4}$alkyl; and

$R^3$, $R^4$ and $R^5$ are independently selected from fluoro and methyl.

Another embodiment of the invention provides a compound of formula I, wherein

G is selected from –O- and –$CF_2$-;

$R^1$ and $R^2$ are independently selected from –H, hydroxy, methyl, 2-hydroxylethyl; and

$R^3$, $R^4$ and $R^5$ are independently selected from fluoro and methyl.

A further embodiment of the invention provides a compound of formula I, wherein

G is selected from –O- and –$CF_2$-;

$R^1$ and $R^2$ are independently selected from –H, hydroxy, methyl, 2-hydroxylethyl; and

$R^3$, $R^4$ and $R^5$ are methyl.

An even further embodiment of the invention provides a compound of formula I,

wherein

G is –O-;

$R^1$ and $R^2$ are independently selected from –H, hydroxy, methyl, 2-hydroxylethyl with $R^1$ and $R^2$ being different groups; and

$R^3$, $R^4$ and $R^5$ are methyl.

A further embodiment of the invention provides a compound of formula I, wherein

G is $–CF_2$-;

$R^1$ and $R^2$ are independently selected from –H, hydroxy, methyl, 2-hydroxylethyl with $R^1$ and $R^2$ being different groups; and

$R^3$, $R^4$ and $R^5$ are methyl.

In another embodiment, $R^1$ and $R^2$ of formula I together with the nitrogen linked thereto form a $C_{2-5}$cycloheteroalkyl.

In a further embodiment, $R^1$ and $R^2$ of formula I together with the nitrogen linked thereto form a $C_{2-5}$cycloheteroalkyl selected from morpholinyl, isoxazolidinyl, and azetindinyl.

In another embodiment, $R^1$ and $R^2$ of formula I are independently selected from –H, hydroxy, $C_{1-4}$alkyl, $C_{3-6}$cycloalkyl, $C_{1-4}$alkoxy-$C_{1-4}$alkyl, $C_{1-4}$alkoxy, and hydroxy-$C_{1-4}$alkyl.

In another embodiment, G of formula I is $–CF_2$-.

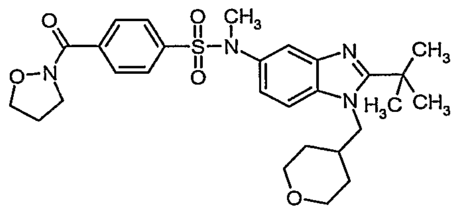
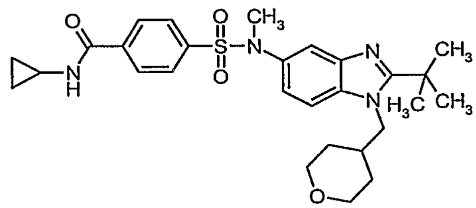
In another embodiment, G of formula I is –O-.

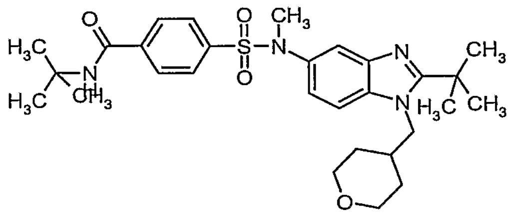
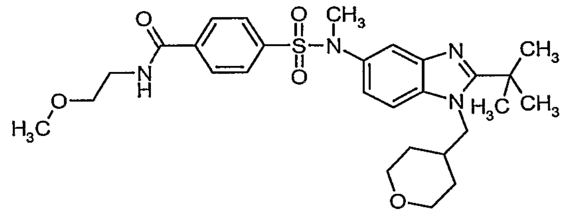
In another embodiment, G of formula I is –CHF-.

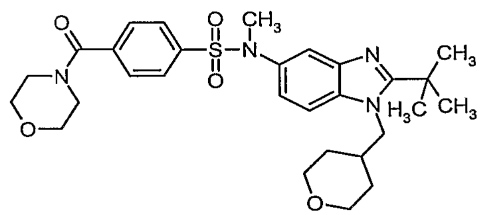
In another embodiment, $R^3$, $R^4$ and $R^5$ are methyl.

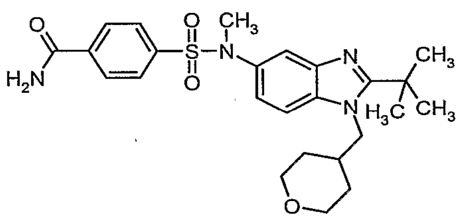
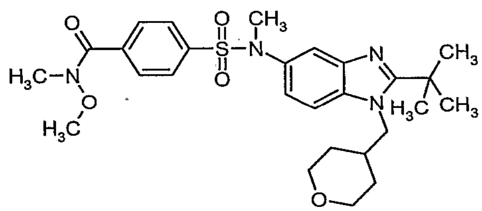
In another embodiment, $R^3$, $R^4$ and $R^5$ are –F.

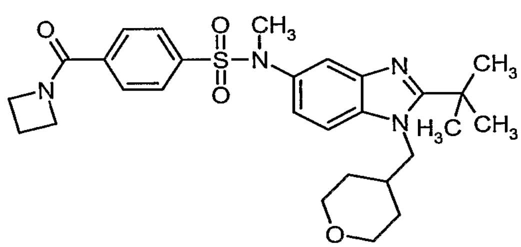
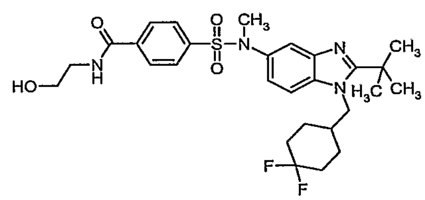
A further embodiment of the invention provides a compound selected from

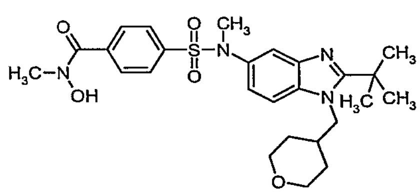
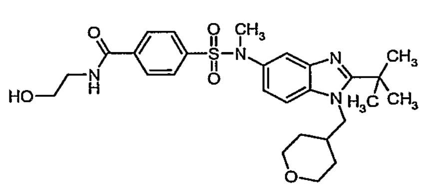
 ,  ,

 ,  ,

 ,

 ,  ,

 ,  ,

 ,  , and

pharmaceutically acceptable salts thereof.

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The

present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present invention includes any geometrical isomer of a compound of Formula I. It will further be understood that the present invention encompasses tautomers of the compounds of the Formula I.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of the Formula I.

Within the scope of the invention are also salts of the compounds of the Formula I. Generally, pharmaceutically acceptable salts of compounds of the present invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

In one embodiment, the compound of Formula I above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

We have now found that the compounds of the invention have activity as pharmaceuticals, in particular as modulators or ligands such as agonists, partial agonists, inverse agonist or antagonists of $CB_1$ receptors. More particularly, the

compounds of the invention exhibit selective activity as agonist of the $CB_1$ receptors and are useful in therapy, especially for relief of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive. Additionally, compounds of the present invention are useful in other disease states in which dysfunction of $CB_1$ receptors is present or implicated. Furthermore, the compounds of the invention may be used to treat cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and cardiovascular disorders.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of cannabinoid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety and stress-related disorders such as post-traumatic stress disorders, panic disorder, generalized anxiety disorder, social phobia, and obsessive compulsive disorder, urinary incontinence, premature ejaculation, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, e.g. constipation, functional gastrointestinal disorders such as Irritable Bowel Syndrome and Functional Dyspepsia, Parkinson's disease and other motor disorders, traumatic brain injury, stroke, cardioprotection following miocardial infarction, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (e.g. amnesia, analgesia, muscle relaxation and sedation).

Included in this combination are inhaled anaesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

Also within the scope of the invention is the use of any of the compounds according to the Formula I above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the Formula I above, is administered to a patient in need of such treatment.

Thus, the invention provides a compound of Formula I or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be contrued accordingly. The term "therapy" within the context of the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

The compounds of the present invention are useful in therapy, especially for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

In use for therapy in a warm-blooded animal such as a human, the compound of the invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, transdermally, intracerebroventricularly and by injection into the joints.

In one embodiment of the invention, the route of administration may be oral, intravenous or intramuscular.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid and liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or table disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture in then poured into convenient sized moulds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (per cent by weight), more preferably from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

Within the scope of the invention is the use of any compound of Formula I as defined above for the manufacture of a medicament.

Also within the scope of the invention is the use of any compound of Formula I for the manufacture of a medicament for the therapy of pain.

Additionally provided is the use of any compound according to Formula I for the manufacture of a medicament for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the Formula I above, is administered to a patient in need of such therapy.

Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

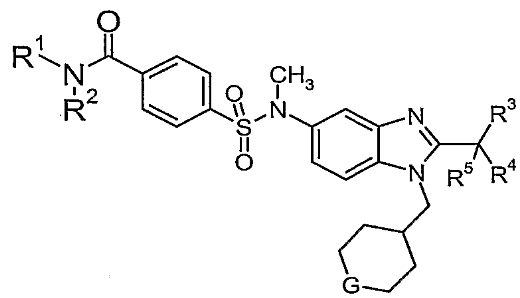
Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association

with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of pain.

Further, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

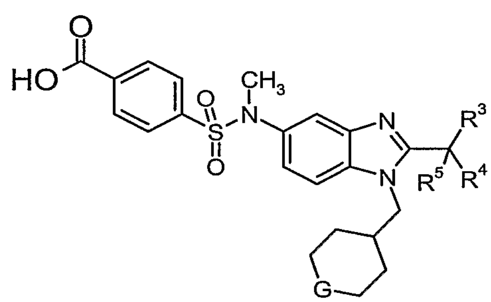
In a further aspect, the present invention provides a method of preparing the compounds of the present invention.

In one embodiment, the invention provides a process for preparing a compound of Formula I, comprising:



I

reacting a compound of Formula II with $HNR^1R^2$,



II

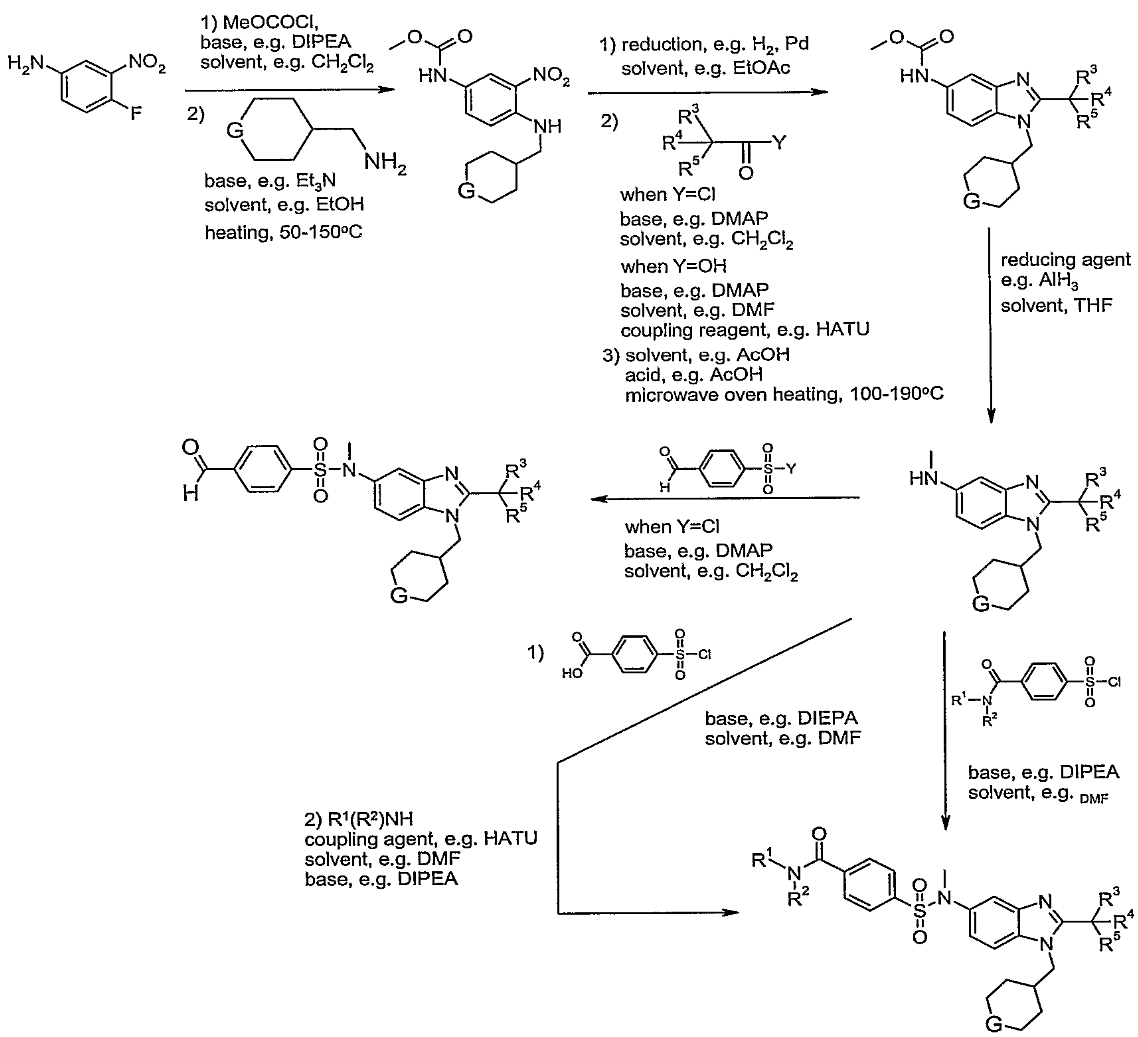
wherein G, $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are as defined above.

Another embodiment of the method of preparing a compound of formula I includes reacting a compound of formula II with $HNR^1R^2$ in the presence of at least one coupling reagent..

In a further embodiment, the method of preparing a compound of formula I include reacting a compound of formula II with $HNR^1R^2$ in the presence of one coupling reagent, wherein said reagent is selected from HATU and EDC.

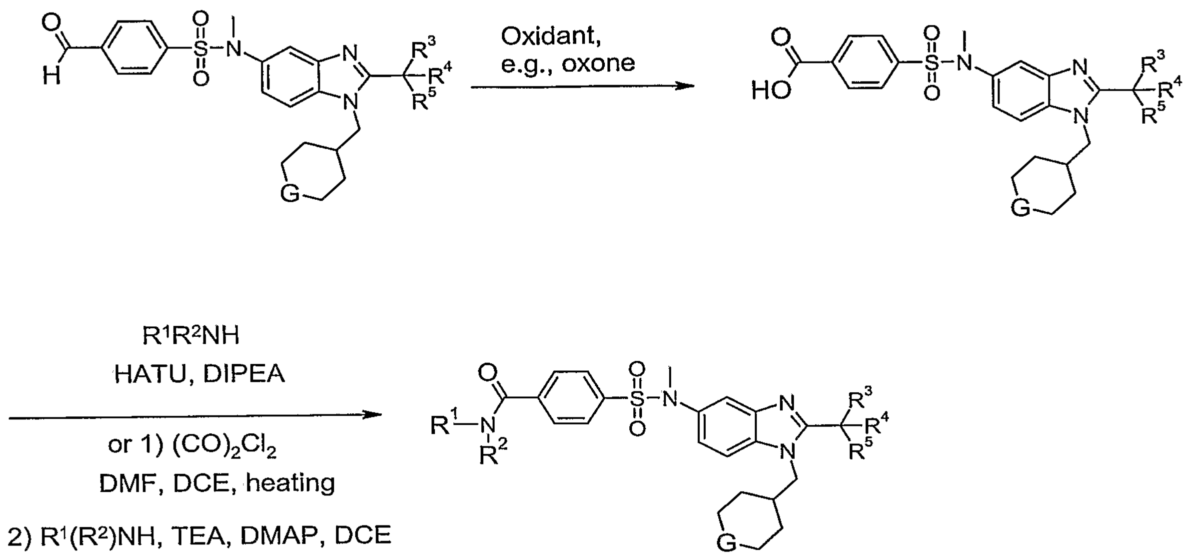
Compounds of the present invention may also be prepared according to the synthetic routes as depicted in Schemes 1 and 2.

**Scheme 1**




G, $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are as defined above.

**Scheme 2**




G, $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are as defined above.

## Biological Evaluation

### hCB$_1$ and hCB$_2$ receptor binding

Human CB$_1$ receptor from Receptor Biology (hCB$_1$) or human CB$_2$ receptor from BioSignal (hCB$_2$) membranes are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle, diluted in the cannabinoid binding buffer (50 mM Tris, 2.5 mM EDTA, 5 mM $MgCl_2$, and 0.5 mg/mL BSA fatty acid free, pH 7.4) and aliquots containing the appropriate amount of protein are distributed in 96-well plates. The $IC_{50}$ of the compounds of the invention at hCB$_1$ and hCB$_2$ are evaluated from 10-point dose-response curves done with $^3$H-CP55,940 at 20000 to 25000 dpm per well (0.17-0.21 nM) in a final volume of 300 µl. The total and non-specific binding are determined in the absence and presence of 0.2 µM of HU210 respectively. The plates are vortexed and incubated for 60 minutes at room temperature, filtered through Unifilters GF/B (presoaked in 0.1% polyethyleneimine) with the Tomtec or Packard harvester using 3 mL of wash buffer (50 mM Tris, 5 mM $MgCl_2$, 0.5 mg BSA pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid.

### hCB$_1$ and hCB$_2$ GTPγS binding

Human $CB_1$ receptor from Receptor Biology ($hCB_1$) or human $CB_2$ receptor membranes (BioSignal) are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle and diluted in the GTPγS binding buffer (50 mM Hepes, 20 mM NaOH, 100 mM NaCl, 1 mM EDTA, 5 mM $MgCl_2$, pH 7.4, 0.1% BSA). The $EC_{50}$ and $E_{max}$ of the compounds of the invention are evaluated from 10-point dose-response curves done in 300μl with the appropriate amount of membrane protein and 100000-130000 dpm of $GTPg^{35}S$ per well (0.11 –0.14 nM). The basal and maximal stimulated binding is determined in absence and presence of 1 μM ($hCB_2$) or 10 μM ($hCB_1$) Win 55,212-2 respectively. The membranes are pre-incubated for 5 minutes with 56.25 μM (hCB2) or 112.5 μM ($hCB_1$) GDP prior to distribution in plates (15 μM ($hCB_2$) or 30 μM ($hCB_1$) GDP final). The plates are vortexed and incubated for 60 minutes at room temperature, filtered on Unifilters GF/B (presoaked in water) with the Tomtec or Packard harvester using 3 ml of wash buffer (50 mM Tris, 5 mM $MgCl_2$, 50 mM NaCl, pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 μl/well of MS-20 scintillation liquid. Antagonist reversal studies are done in the same way except that (a) an agonist dose-response curve is done in the presence of a constant concentration of antagonist, or (b) an antagonist dose-response curve is done in the presence of a constant concentration of agonist.

Based on the above assays, the dissociation constant (Ki) for a particular compound of the invention towards a particular receptor is determined using the following equation:

$$Ki = IC_{50}/(1+[rad]/Kd),$$

Wherein $IC_{50}$ is the concentration of the compound of the invention at which 50% displacement has been observed;

[rad] is a standard or reference radioactive ligand concentration at that moment; and

Kd is the dissociation constant of the radioactive ligand towards the particular receptor.

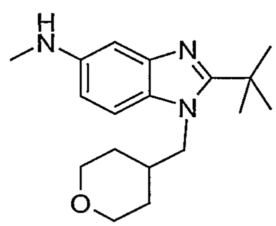
Using the above-mentioned assays, the Ki towards human $CB_1$ receptors for certain compounds of the invention are in the range of between 3 nM and 404 nM. EC50 for these compounds are in the range of between 1 nM and 278 nM. Emax for these compounds are in the range of between 122% and 154%.

## EXAMPLES

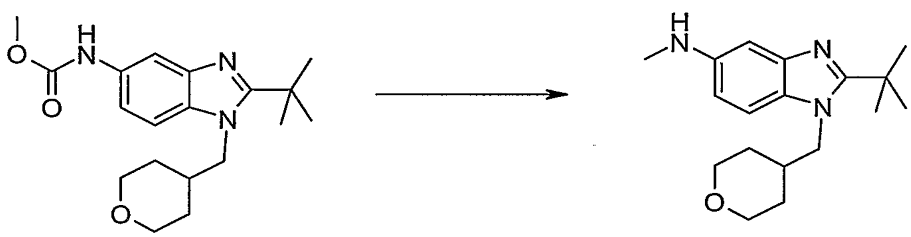
The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

**Example 1**

**2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine**



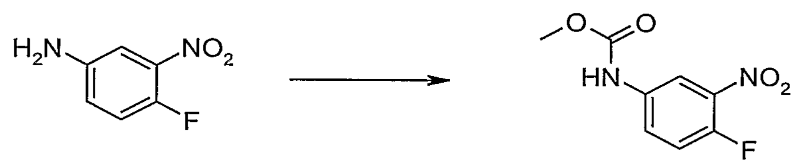
**Step A: 2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine**



Methyl [2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]carbamate (1.80g, 5.21 mmol) (for preparation, see Steps B to E) was dissolved in 75 mL of THF at 0°C. 1M HCl/ether (7.3 mL, 7.29 mmol) was added dropwise and the solution was stirred at 0°C for 15 min. $LiAlH_4$ (988 mg, 26.1 mmol) was added slowly and the solution was stirred at rt overnight. The reaction was quenched at 0°C by addition of MeOH (5 mL) followed by water (10 mL) and the solution was left to stir at rt for 30 min. Anhydrous $Na_2SO_4$ (10 g) was added and the solution was stirred at rt for another 30 min. The solution was filtered and the solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated. Yield: 1.54g

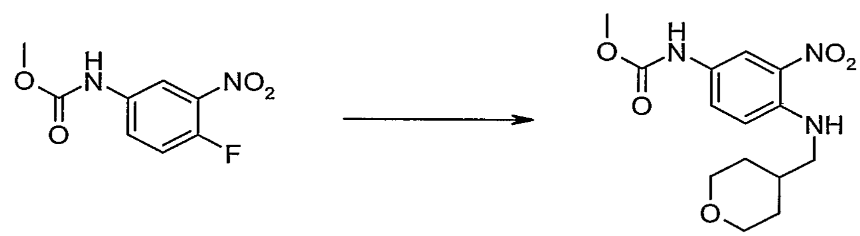
(98%); $^1$H NMR (400 MHz, CHLOROFORM-D): δ 1.49 - 1.53 (m, 4 H), 1.53 - 1.57 (m, 9 H), 2.22 - 2.32 (m, 1 H), 2.87 (s, 3 H), 3.26 - 3.35 (m, 2 H), 3.95 (t, *J*=3.03 Hz, 1 H), 3.97 - 4.00 (m, 1 H), 4.13 (d, *J*=7.42 Hz, 2 H), 6.61 (dd, *J*=8.59, 2.15 Hz, 1 H), 6.99 (d, *J*=1.95 Hz, 1 H), 7.11 (d, *J*=8.59 Hz, 1 H).

**Step B: Methyl (4-fluoro-3-nitrophenyl)carbamate**



Methyl chloroformate (13.2 mL, 170.2 mmol) was added dropwise to a cold (0°C) dichloromethane (200 mL) solution of 4-fluoro-3-nitro aniline (24.15 g, 154.7 mmol) and DIPEA (35 mL, 201 mmol). The reaction mixture was stirred at rt overnight. The solution was then diluted with 200 mL of dichloromethane and washed with 2M HCl, brine and dried over anhydrous $MgSO_4$. The solvent was concentrated and the product was directly used for next step without further purification. Yield: 35.5 g (99%); $^1$H NMR (400 MHz, CHLOROFORM-D): δ 3.81 (s, 3H), 7.02 (s, 1H), 7.23 (m, 1H), 7.72 (d, J = 8.59Hz, 1H), 8.17 (dd, J = 6.35, 2.64Hz, 1H).

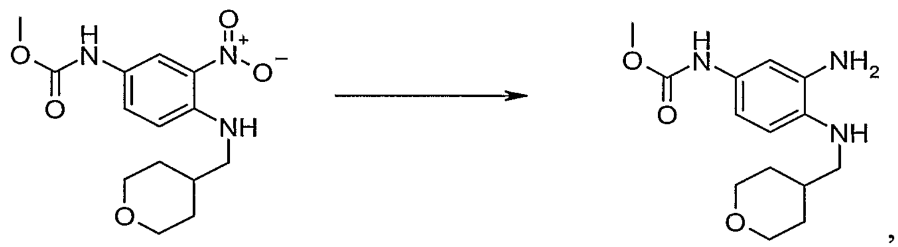
**Step C. Methyl {3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}carbamate**



Methyl (4-fluoro-3-nitrophenyl)carbamate (2.0 g, 9.32 mmol) and 4-aminomethyl tetrahydropyran (1.28g, 11.2 mmol) were stirred in 50 mL of EtOH containing TEA (2.0 mL, 14.0 mmol) at 75°C for 48 h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous 5% $KHSO_4$, saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using 1:1 / hexanes : EtOAc as eluent. Yield: 2.53 g (88%); $^1$H NMR (400 MHz, CHLOROFORM-D): δ 1.42 (ddd,

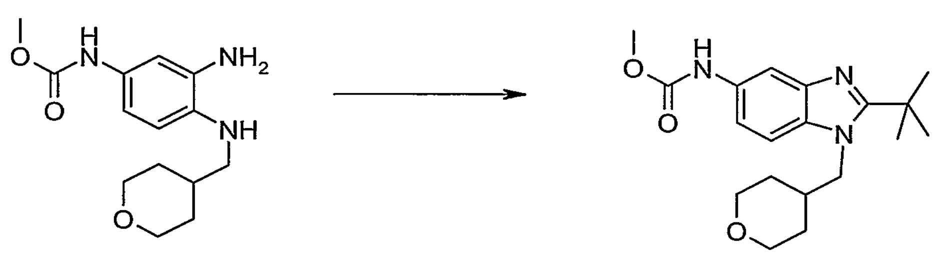
*J*=25.24, 12.06, 4.49 Hz, 2 H), 1.73 (d, *J*=1.76 Hz, 1 H), 1.76 (d, *J*=1.95 Hz, 1 H), 1.88 - 2.01 (m, 1 H), 3.22 (dd, *J*=6.74, 5.57 Hz, 2 H), 3.42 (td, *J*=11.86, 2.05 Hz, 2 H), 3.78 (s, 3 H), 4.01 (d, *J*=4.30 Hz, 1 H), 4.04 (d, *J*=3.51 Hz, 1 H), 6.48 (br.s, 1 H), 6.85 (d, *J*=9.37 Hz, 1 H), 7.65 (br.s, 1 H), 8.03 - 8.09 (m, 2 H).

**Step D. Methyl {3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}carbamate**



Methyl {3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}carbamate (2.53 g, 8.18 mmol) was dissolved in 50 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken under $H_2$ atmosphere (40 psi) using a Parr hydrogenation apparatus overnight at rt. The solution was filtered through celite and the solvent was evaporated. Yield: 2.29 g (99%); $^1$H NMR (400 MHz, CHLOROFORM-D): δ 1.40 (ddd, *J*=25.09, 12.01, 4.49 Hz, 2 H), 1.70 - 1.74 (m, 1 H), 1.74 - 1.77 (m, 1 H), 1.81 - 1.92 (m, 1 H), 2.99 (d, *J*=6.64 Hz, 2 H), 3.34 (br.s, 2 H), 3.41 (dt, *J*=11.81, 2.15 Hz, 2 H), 3.74 (s, 3 H), 3.99 (d, *J*=3.51 Hz, 1 H), 4.02 (d, *J*=3.51 Hz, 1 H), 6.38 (br.s, 1 H), 6.55 - 6.60 (m, 1 H), 6.62 - 6.68 (m, 1 H), 6.95 (br.s, 1 H).

**Step E. Methyl [2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]carbamate**

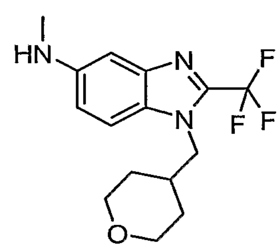


Methyl {3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}carbamate (2.29 g, 8.20 mmol) and DMAP (0.20 g, 1.64 mmol) were dissolved in 75 mL of DCM.

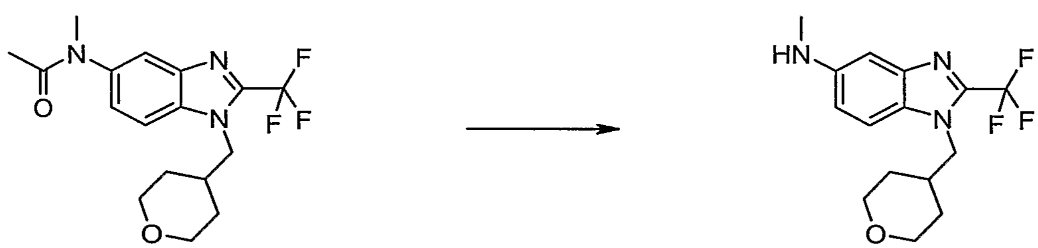
Trimethylacetyl chloride (1.10 mL, 9.02 mmol) was added dropwise and the solution was stirred at rt for 2h. The solution was washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The residue was dissolved in 25 mL of AcOH and was heated at 125°C for 1h using a Personal Chemistry microwave apparatus. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using 4:3 / hexanes : acetone as eluent. Yield: 1.81 g (64%); $^1$H NMR (400 MHz, CHLOROFORM-D): δ 1.48 - 1.54 (m, 4 H) 1.56 (s, 9 H) 2.23 - 2.35 (m, 1 H) 3.27 - 3.35 (m, 2 H) 3.78 (s, 3 H) 3.96 (t, *J*=2.93 Hz, 1 H) 3.99 (t, *J*=3.03 Hz, 1 H) 4.18 (d, *J*=7.42 Hz, 2 H) 6.63 (br.s, 1 H) 7.24 - 7.28 (m, 1 H) 7.41 (br.s, 1 H) 7.61 (d, *J*=1.95 Hz, 1 H).

**Example 2**

***N*-Methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-amine**



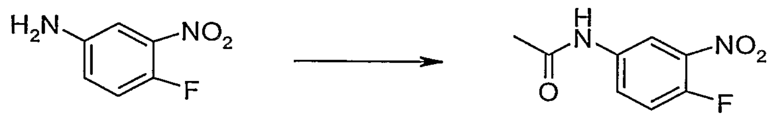
**Step A. *N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-amine**



The crude *N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]acetamide (~500 mg, 1.42 mmol) (for preparation, see Steps B to F) was dissolved in 10 mL of EtOH-2*N* HCl (3:2), and then heated at 120°C in a Personal Chemistry SmithSynthesizer microwave instrument for 4 h. After

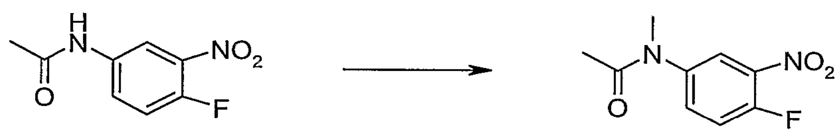
concentration and dried *in vacuo*, 539 mg (100%) of a grey white solid was obtained as the title product, which was used directly for Step A. MS (ESI) $(M+H)^+ = 314.20$.

**Step B. *N*-(4-fluoro-3-nitrophenyl)acetamide**



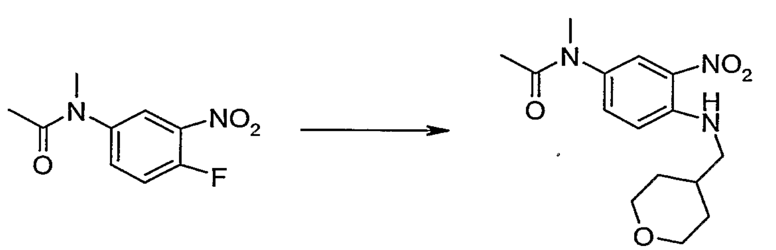
4-Fluoro-3-nitro-aniline (45.0 g, 0.288 mol) was added in portions to acetic anhydride (150 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The white solid was collected and dried *in vacuo* to give the title compound (42.0 g, 70%). $^1H$ NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 3 H), 7.26 (m, 1 H), 7.50 (s broad, 1 H), 7.87 (m, 1 H), 8.23 (dd, *J*=6.44, 2.73 Hz, 1 H).

**Step C. *N*-(4-fluoro-3-nitrophenyl)-*N*-methylacetamide**



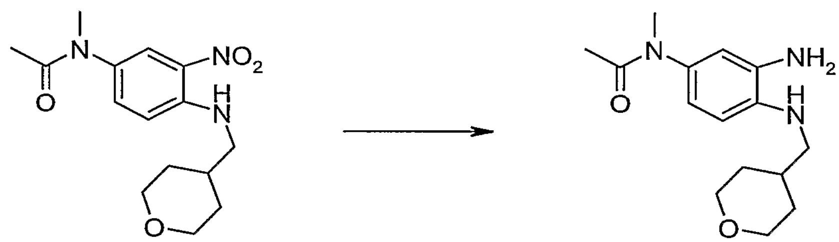
Sodium hydride (2.40 g, 60 mmol) was added in portions to a solution of *N*-(4-fluoro-3-nitrophenyl)acetamide (7.93 g, 40 mmol) in THF (120 mL) at 0 °C. Stirring for 20 min, iodomethane (17.0 g, 120 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, quenched with saturaed $NaHCO_3$ (30 mL) and extracted with EtOAc (3x100 mL). The combined organic phases were washed with saturated NaCl (2x30 mL). After filtration and concentration, 8.73 g (100%) of the title compound was obtained as a brown solid. $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.92 (s, 3 H), 3.30 (s, 3 H), 7.38 (s, 1 H), 7.52 (s, 1 H), 7.95 (s, 1 H).

**Step D. *N*-methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide**



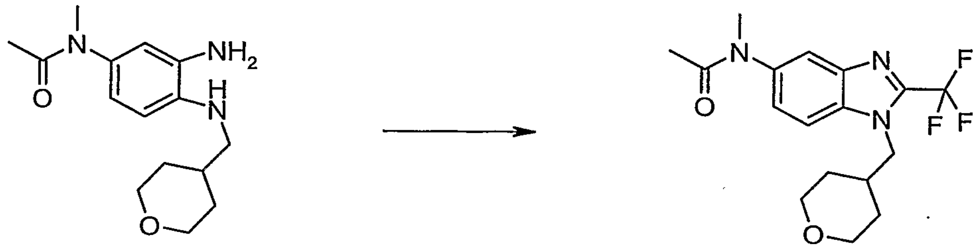
4-Aminomethyltetrahydropyran (2.50 g, 21.7 mmol ) was added to a mixture of *N*-(4-fluoro-3-nitrophenyl)-*N*-methylacetamide (4.61 g, 21.27 mmol) and sodium carbonate (5.10 g, 47.7 mmol) in EtOH (120 mL) at room temperature. The reaction mixture was heated for 3 days at 60 °C. Upon evaporation of ethanol, the residue was dissolved in EtOAc (400 mL), washed with $H_2O$ (3x50 mL), saturated NaCl (3x50 mL), and dried over $Na_2SO_4$. After filtation and concentration, 6.62 g (100%) of the title compound was obtained as an orange-red solid. $^1$H NMR (400 MHz, $CDCl_3$): δ 1.38 - 1.52 (m, 2 H), 1.72 - 1.81 (m, 2 H), 1.90 (s, 3 H), 1.93 - 2.02 (m, 1 H), 3.23 (s, 3 H), 3.23 - 3.27 (m, 2 H), 3.36 - 3.49 (m, 2 H), 4.01 - 4.07 (m, 2 H), 6.91 (d, *J*=9.18 Hz, 1 H), 7.29 (dd, *J*=9.08, 2.64 Hz, 1 H), 8.05 (d, *J*=2.34 Hz, 1 H), 8.22 (t, *J*=5.37 Hz, 1 H). MS (ESI) $(M+H)^+$ = 309.12.

**Step E. *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide**



*N*-methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide (5.39 g, 16.7 mmol) was hydrogenated in ethyl acetate (200 mL) catalyzed by 10% Pd/C (0.2 g) at 30-40 psi $H_2$ in Parr shaker for 18 h at room temperature. After filtration through celite and concentration, 6.0 g (100%) of a purple solid was obtained as HCl salt, which was used in the next step without purification. $^1$H NMR (400 MHz, $CD_3OD$): δ 1.32 - 1.46 (m, 2 H), 1.78 - 1.84 (m, 2 H), 1.85 (s, 3 H), 1.91 - 2.06 (m, 1 H), 3.16 (d, *J*=6.83 Hz, 2 H), 3.20 (s, 3 H), 3.39 - 3.51 (m, 2 H), 3.94 - 4.03 (m, 2 H), 7.01 (d, *J*=8.59 Hz, 1 H), 7.12 (d, *J*=2.15 Hz, 1 H), 7.17 (dd, *J*=8.49, 4.39 Hz, 1 H). MS (ESI) $(M+H)^+$ = 278.7

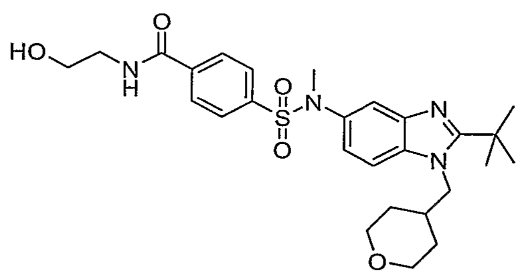
**Step F. *N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]acetamide**



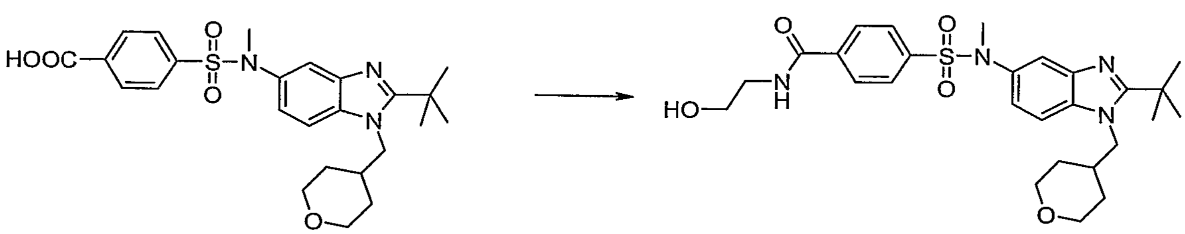
A solution of *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide hydrochoride (395.1 mg, 1.42 mmol) in trifluoroacetic acid (10 mL) was heated to reflux for 20 h. After evaporation of the solvent, the crude product was used directly for next step without purification. MS (ESI) $(M+H)^+$: 356.02.

**Example 3**

**4-{[[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}-N-(2-hydroxyethyl)benzamide**



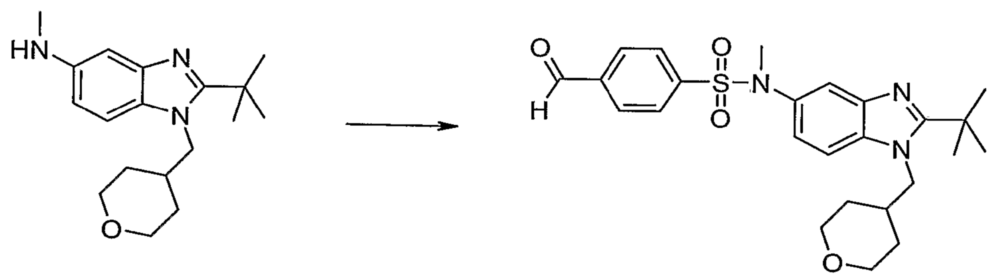
**Step A: 4-{[[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}-N-(2-hydroxyethyl)benzamide**



4-{[[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}benzoic acid (for preparation, see following Steps B and C) (550 mg, 1.13 mmol), HATU (516 mg, 1.36 mmol), DIPEA (0.300 mL, 1.70 mmol) and ethanolamine (0.100 mL, 1.70 mmol) were stirred in 75 mL of DMF at rt

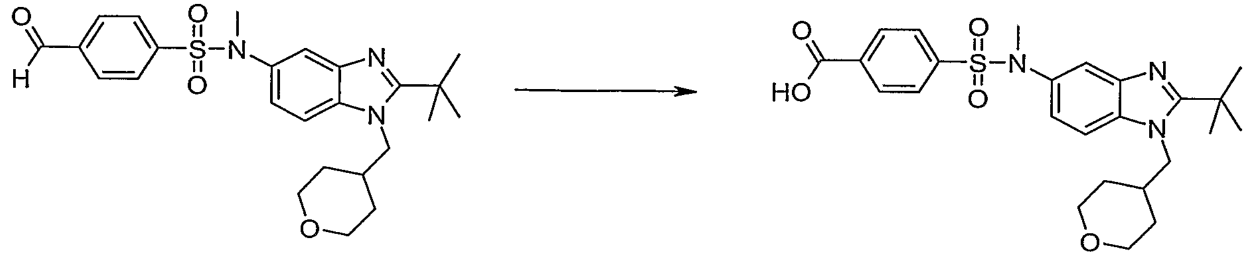
for 3h. Another 2.2 mmol of HATU (860 mg) and ethanolamine (0.130 mL) were added and the solution stirred at rt overnight. The solvent was evaporated. The residue was dissolved in DCM and washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% $CH_3CN/H_2O$ and lyophilized affording the title compound as the corresponding TFA salt. Yield: 450 mg (62%). $^1$H NMR (400 MHz, METHANOL-$D_4$) δ 1.50 - 1.55 (m, 2 H), 1.56 - 1.64 (m, 2 H), 1.67 (s, 9 H), 2.31 - 2.41 (m, 1 H), 3.29 (s, 3 H), 3.35 (td, *J*=11.67, 2.64 Hz, 2 H), 3.51 (t, *J*=5.76 Hz, 2 H), 3.71 (t, *J*=5.76 Hz, 2 H), 3.93 (d, *J*=3.12 Hz, 1 H, 3.95 - 3.98 (m, 1 H), 4.51 (d, *J*=7.42 Hz, 2 H), 7.29 (dd, *J*=8.98, 2.15 Hz, 1 H), 7.51 (d, *J*=1.76 Hz, 1 H), 7.62 (d, *J*=8.79 Hz, 2 H), 7.85 (d, *J*=9.18 Hz, 1 H), 7.95 (d, *J*=8.59 Hz, 2 H); MS (ESI) $(M+H)^+$ 529.0.

**Step B: N-[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-4-formyl-N-methylbenzenesulfonamide**



2-*tert*-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (for preparation, see Steps B to F of Example 1) (500 mg, 1.66 mmol) and DMAP (40 mg, 0.332 mmol) were dissolved in 50 mL of DCM. 4-Formylbenzenesulfonyl chloride (407 mg, 1.99 mmol) was added and the solution was stirred at rt for 4h. The solution was washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by silica gel flash chromatography using 65% to 100% EtOAc / hexanes. Yield: 620 mg (80%); $^1$H NMR (400 MHz, CHLOROFORM-D) δ 1.50 - 1.57 (m, 13 H), 2.25 - 2.35 (m, 1 H), 3.26 (s, 3 H), 3.30 - 3.38 (m, 2 H), 3.99 (t, *J*=3.03 Hz, 1 H), 4.02 (t, *J*=2.93 Hz, 1 H), 4.20 (d, *J*=7.42 Hz, 2 H), 7.19 - 7.22 (m, 1 H), 7.23 (d, *J*=2.15 Hz, 1 H), 7.28 - 7.32 (m, 1 H), 7.76 (d, *J*=8.20 Hz, 2 H), 7.96 (d, *J*=8.59 Hz, 2 H), 10.10 (s, 1 H).

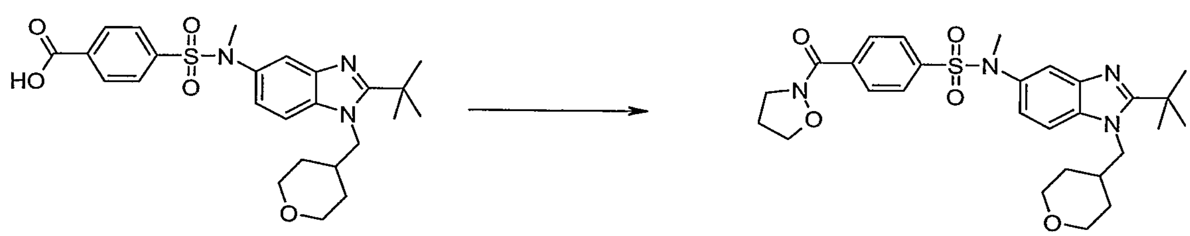
**Step C: 4-{[[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}benzoic acid**



N-[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-4-formyl-N-methylbenzenesulfonamide (620 mg, 1.32 mmol) was dissolved in 50 mL of DMF. Oxone (1.22 g, 1.98 mmol) was added and the solution was heated at 50°C for 48h. The solvent was evaporated. The residue was dissolved in water and extracted 3X with DCM. The organic phases were combined and washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated. Yield: 623 mg (97%); $^1$H NMR (400 MHz, CHLOROFORM-D) δ 1.54 - 1.61 (m, 13 H), 2.27 - 2.37 (m, 1 H), 3.24 (s, 3 H), 3.32 - 3.40 (m, 2 H), 3.99 - 4.02 (m, 1 H), 4.03 - 4.06 (m, 1 H), 4.26 (d, *J*=7.42 Hz, 2 H), 7.39 - 7.44 (m, 2 H), 7.47 - 7.52 (m, 1 H), 7.73 (d, *J*=8.59 Hz, 2 H), 8.19 (d, *J*=8.40 Hz, 2 H).

**Example 4**

***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(isoxazolidin-2-ylcarbonyl)-*N*-methylbenzenesulfonamide**

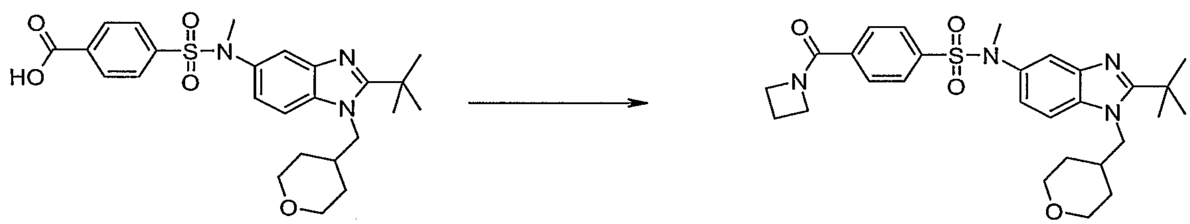


4-{[[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}benzoic acid (50 mg, 0.103 mmol) was suspended in 8 mL of DCE containing a drop of DMF. Oxalyl chloride (0.012 mL, 0.134 mmol) was added dropwise and the solution was stirred at 40°C for 1h. A solution of isoxazolidine hydrochloride (23 mg, 0.206 mmol) and TEA (0.045 mL, 0.309 mmol)

in 2 mL of DCM was added dropwise and the solution was stirred at rt for 1h. The solution was washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% $CH_3CN/H_2O$ and lyophilized affording the title compound as the corresponding TFA salt. Yield: 48 mg (71%). $^1$H NMR (400 MHz, METHANOL-$D_4$) δ 1.49 - 1.55 (m, 2 H), 1.55 - 1.62 (m, 2 H), 1.66 (s, 9 H), 2.31 - 2.35 (m, 1 H), 2.37 - 2.43 (m, 2 H), 3.28 - 3.28 (m, 3 H), 3.33 (td, *J*=11.47, 2.64 Hz, 2 H), 3.83 - 3.88 (m, 2 H), 3.91 (d, *J*=3.32 Hz, 1 H), 3.92 - 3.95 (m, 1 H), 4.03 (t, *J*=6.74 Hz, 2 H), 4.51 (d, *J*=7.42 Hz, 2 H), 7.31 (dd, *J*=8.98, 2.15 Hz, 1 H), 7.54 (d, *J*=1.76 Hz, 1 H), 7.58 (d, *J*=8.59 Hz, 2 H), 7.83 (d, *J*=8.59 Hz, 2 H), 7.88 (d, *J*=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 541.0; Anal. Calcd(%) for $C_{28}H_{36}N_4O_5S$ + 2.0 TFA + 0.3 $H_2O$: C, 49.65; H, 5.03; N, 7.24. Found: C, 49.57; H, 4.99; N, 7.38.

**Example 5**

**4-(Azetidin-1-ylcarbonyl)-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide**

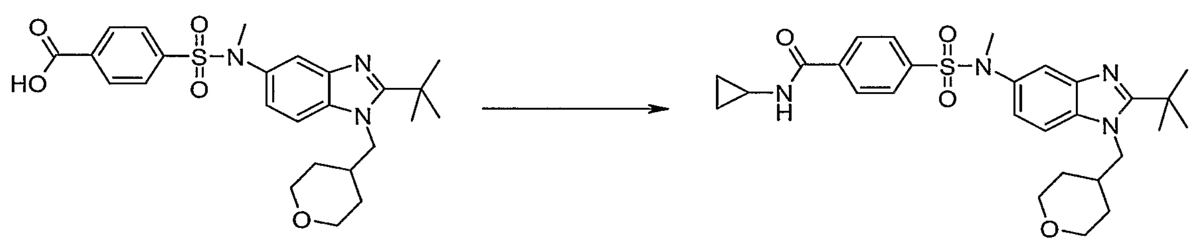


4-{[[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}benzoic acid (50 mg, 0.103 mmol) was suspended in 8 mL of DCE containing a drop of DMF. Oxalyl chloride (0.012 mL, 0.134 mmol) was added dropwise and the solution was stirred at 40°C for 1h. A solution of azetidine (12 mg, 0.206 mmol) and TEA (0.045 mL, 0.309 mmol) in 2 mL of DCM was added dropwise and the solution was stirred at rt for 1h. The solution was washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% $CH_3CN/H_2O$ and lyophilized affording the title compound as the corresponding TFA salt. Yield: 34 mg (52%). $^1$H NMR (400 MHz, METHANOL-$D_4$) δ 1.48 - 1.54 (m, 2 H), 1.54 - 1.62 (m,

2 H), 1.65 (s, 9 H), 2.30 - 2.41 (m, 3 H), 3.27 (s, 3 H), 3.33 (td, *J*=11.62, 2.73 Hz, 2 H), 3.91 (d, *J*=2.93 Hz, 1 H), 3.92 - 3.96 (m, 1 H), 4.18 (t, *J*=7.91 Hz, 2 H), 4.33 (t, *J*=7.71 Hz, 2 H), 4.49 (d, *J*=7.42 Hz, 2 H), 7.27 (dd, *J*=9.08, 2.05 Hz, 1 H), 7.51 (d, *J*=1.56 Hz, 1 H), 7.60 (d, *J*=8.59 Hz, 2 H), 7.73 (d, *J*=8.79 Hz, 2 H), 7.85 (d, *J*=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 525.0; Anal. Calcd(%) for $C_{28}H_{36}N_4O_4S$ + 1.4 TFA + 0.1 $H_2O$: C, 53.92; H, 5.52; N, 8.17. Found: C, 53.92; H, 5.51; N, 7.77.

**Example 6**

**4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropylbenzamide**

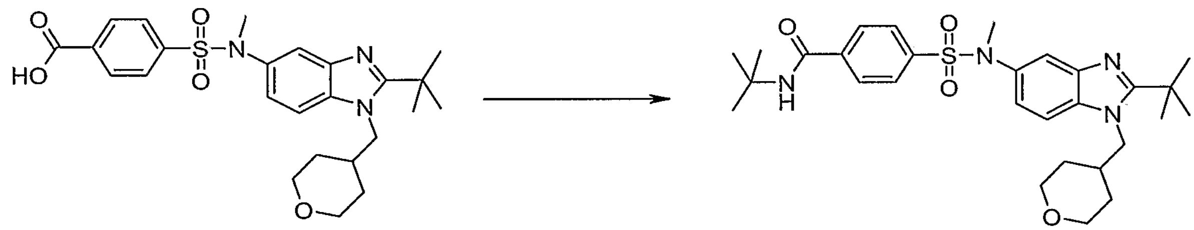


4-{[[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}benzoic acid (55 mg, 0.113 mmol) was suspended in 10 mL of DCE containing a drop of DMF. Oxalyl chloride (0.019 mL, 0.147 mmol) was added dropwise and the solution was stirred at 40°C for 1h. A solution of cyclopropylamine (0.016 mL, 0.226 mmol) and TEA (0.040 mL, 0.283 mmol) in 1 mL of DCM was added dropwise and the solution was stirred at rt for 1h. The solution was washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% $CH_3CN/H_2O$ and lyophilized affording the title compound as the corresponding TFA salt. Yield: 49 mg (68%). $^1$H NMR (400 MHz, METHANOL-$D_4$) δ 0.58 - 0.64 (m, 2 H), 0.77 - 0.83 (m, 2 H), 1.48 - 1.54 (m, 2 H), 1.54 - 1.62 (m, 2 H), 1.65 (s, 9 H), 2.30 - 2.38 (m, 1 H), 2.80 - 2.87 (m, 1 H), 3.27 (s, 3 H), 3.33 (td, *J*=11.57, 2.64 Hz, 2 H), 3.91 (d, *J*=3.32 Hz, 1 H), 3.94 (d, *J*=2.15 Hz, 1 H), 4.50 (d, *J*=7.42 Hz, 2 H), 7.27 (dd, *J*=8.98, 2.15 Hz, 1 H), 7.50 (d, *J*=1.56 Hz, 1 H), 7.58 (d, *J*=8.59 Hz, 2 H), 7.85 (d, *J*=9.18 Hz, 1 H), 7.88 (d, *J*=8.79 Hz, 2 H); MS (ESI) $(M+H)^+$ 525.0; Anal. Calcd(%)

for $C_{28}H_{36}N_4O_4S$ + 0.6 TFA + 0.3 $H_2O$: C, 58.60; H, 6.27; N, 9.36. Found: C, 58.63; H, 6.14; N, 9.57.

**Example 7**

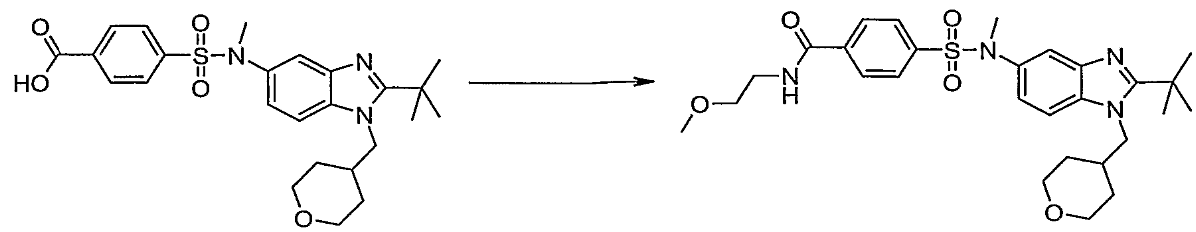
***N*-(*tert*-Butyl)-4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}benzamide**



4-{[[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}benzoic acid (55 mg, 0.113 mmol) was suspended in 10 mL of DCE containing a drop of DMF. Oxalyl chloride (0.019 mL, 0.147 mmol) was added dropwise and the solution was stirred at 40°C for 1h. A solution of tert-butylamine (0.018 mL, 0.170 mmol) and TEA (0.040 mL, 0.283 mmol) in 2 mL of DCM was added dropwise and the solution was stirred at rt for 1h. The solution was washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% $CH_3CN/H_2O$ and lyophilized affording the title compound as the corresponding TFA salt. Yield: 26 mg (35%). $^1$H NMR (400 MHz, METHANOL-$D_4$) δ 1.43 (s, 9 H), 1.47 - 1.54 (m, 2 H), 1.55 - 1.62 (m, 2 H), 1.65 (s, 9 H), 2.30 - 2.38 (m, 1 H), 3.27 (s, 3 H), 3.33 (td, *J*=11.57, 2.44 Hz, 2 H), 3.91 (d, *J*=2.93 Hz, 1 H), 3.94 (d, *J*=3.32 Hz, 1 H), 4.49 (d, *J*=7.42 Hz, 2 H), 7.25 (dd, *J*=8.98, 1.95 Hz, 1 H), 7.49 (d, *J*=1.76 Hz, 1 H), 7.57 (d, *J*=8.79 Hz, 2 H), 7.80 - 7.86 (m, 3 H); MS (ESI) $(M+H)^+$ 541.0.

**Example 8**

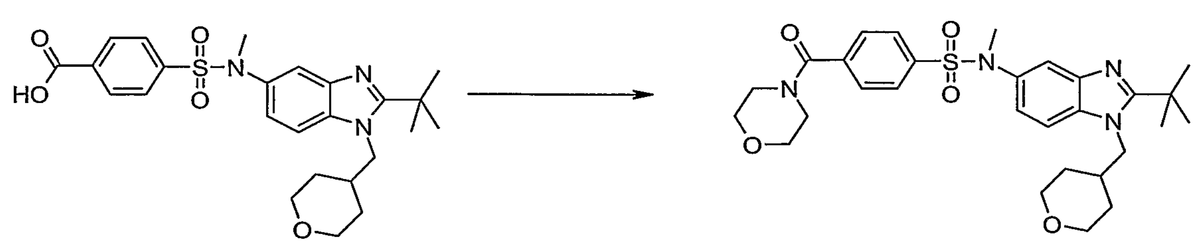
**4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(2-methoxyethyl)benzamide**



4-{[[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}benzoic acid (40 mg, 0.0824 mmol), 2-methoxyethylamine (0.011 mL, 0.123 mmol), DIPEA (0.045 mL, 0.247 mmol) and HATU (38 mg, 0.0989 mmol) were stirred in 5 mL of DMF at rt for 1h. The solvent was evaporated. The product was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% $CH_3CN/H_2O$ and lyophilized affording the title compound as the corresponding TFA salt. Yield: 19 mg (42%). $^1H$ NMR (600 MHz, $CD_3OD$) δ 1.52 - 1.56 (m, 2 H), 1.57 - 1.64 (m, 2 H), 1.68 (s, 9 H), 2.32 - 2.40 (m, 1 H), 3.30 (s, 3 H), 3.32 - 3.38 (m, 5 H), 3.56 (s, 4 H), 3.94 (d, *J*=3.29 Hz, 1 H), 3.95 (d, *J*=3.02 Hz, 1 H), 4.53 (d, *J*=7.68 Hz, 2 H), 7.31 (dd, *J*=8.92, 2.06 Hz, 1 H), 7.54 (d, *J*=1.65 Hz, 1 H), 7.62 (d, *J*=8.78 Hz, 2 H), 7.90 (d, *J*=9.06 Hz, 1 H), 7.93 (d, *J*=8.51 Hz, 2 H); MS (ESI) $(M+H)^+$ 543.0; Anal. Calcd(%) for $C_{28}H_{38}N_4O_5S$ + 2.5 TFA: C, 47.88; H, 4.93; N, 6.77. Found: C, 47.95; H, 4.75; N, 7.04.

**Example 9**

***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(morpholin-4-ylcarbonyl)benzenesulfonamide**

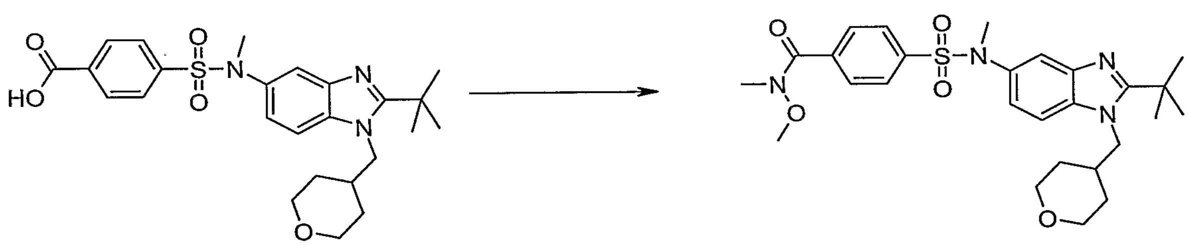


4-{[[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}benzoic acid (72 mg, 0.153 mmol), morpholine (0.016

mL, 0.184 mmol), DIPEA (0.080 mL, 0.459 mmol) and HATU (70 mg, 0.183 mmol) were stirred in 5 mL of DMF at rt for 1h. The solvent was evaporated. The product was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% $CH_3CN/H_2O$ and lyophilized affording the title compound as the corresponding TFA salt. Yield: 52 mg (51%). $^1$H NMR (600 MHz, $CD_3OD$) δ 1.54 - 1.59 (m, 2 H), 1.59 - 1.66 (m, 2 H), 1.71 (s, 9 H), 2.35 - 2.42 (m, 1 H), 3.32 (s, 3 H), 3.35 - 3.40 (m, 3 H), 3.63 (s, 2 H), 3.77 - 3.79 (m, 4 H), 3.96 (d, *J*=3.33 Hz, 1 H), 3.98 (d, *J*=3.58 Hz, 1 H), 4.56 (d, *J*=7.42 Hz, 2 H), 7.35 (dd, *J*=8.96, 2.05 Hz, 1 H), 7.58 - 7.61 (m, 3 H), 7.64 - 7.68 (m, 2 H), 7.92 (d, *J*=8.96 Hz, 1 H); MS (ESI) $(M+H)^+$ 555.0; Anal. Calcd(%) for $C_{29}H_{38}N_4O_5S$ + 2.7 TFA + 0.5 $H_2O$: C, 47.41; H, 4.82; N, 6.43. Found: C, 47.41; H, 4.84; N, 6.45.

**Example 10**

**4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-methoxy-*N*-methylbenzamide**

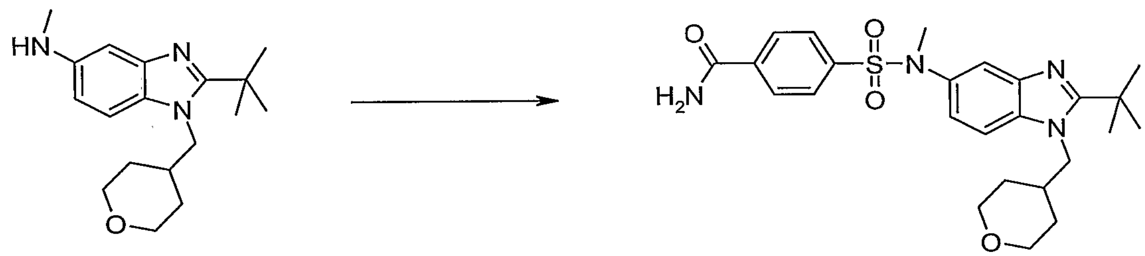


4-{[[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}benzoic acid (50 mg, 0.106 mmol), N,O-dimethylhydroxylamine hydrochloride (12 mg, 0.127 mmol), DIPEA (0.055 mL, 0.318 mmol) and HATU (48 mg, 0.128 mmol) were stirred in 5 mL of DMF at rt for 2h. The solvent was evaporated. The product was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% $CH_3CN/H_2O$ and lyophilized affording the title compound as the corresponding TFA salt. Yield: 36 mg (53%). $^1$H NMR (600 MHz, $CD_3OD$) δ 1.52 - 1.56 (m, 2 H), 1.57 - 1.63 (m, 2 H), 1.68 (s, 9 H), 2.33 - 2.39 (m, 1 H), 3.30 (s, 3 H), 3.33 - 3.38 (m, 5 H), 3.57 (s, 3 H),

3.93 (d, $J$=3.33 Hz, 1 H), 3.95 (d, $J$=3.07 Hz, 1 H), 4.53 (d, $J$=7.42 Hz, 2 H), 7.32 (dd, $J$=8.96, 2.05 Hz, 1 H), 7.57 (d, $J$=1.79 Hz, 1 H), 7.61 (d, $J$=8.45 Hz, 2 H), 7.74 (d, $J$=8.19 Hz, 2 H), 7.90 (d, $J$=8.96 Hz, 1 H); MS (ESI) $(M+H)^+$ 529.0.

**Example 11**

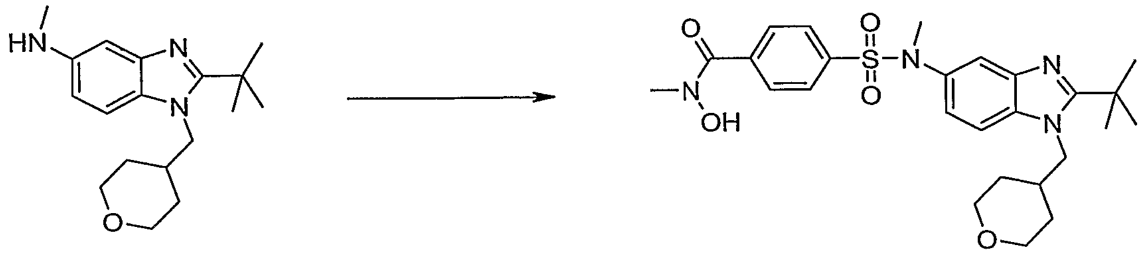
**4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}benzamide**



2-*tert*-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (60 mg, 0.199 mmol) and 4-chlorosulfonyl benzoic acid (57 mg, 0.259 mmol) were stirred in 5 mL of DMF containing DIPEA (0.052 mL, 0.299 mmol) at rt for 3h. Ammonium chloride (53 mg, 0.995 mmol), HATU (90 mg, 0.239 mmol) and DIPEA (0.175 mL, 0.995 mmol) were added and the solution was stirred at rt for 3h. The solvent was evaporated. The product was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% $CH_3CN/H_2O$ and lyophilized affording the title compound as the corresponding TFA salt. Yield: 13 mg (11%). $^1$H NMR (600 MHz, $CD_3OD$) δ 1.54 - 1.59 (m, 2 H), 1.59 - 1.65 (m, 2 H), 1.70 (s, 9 H), 2.35 - 2.41 (m, 1 H), 3.32 (s, 3 H), 3.37 (td, $J$=11.65, 2.30 Hz, 2 H), 3.96 (d, $J$=3.58 Hz, 1 H), 3.98 (d, $J$=3.58 Hz, 1 H), 4.55 (d, $J$=7.68 Hz, 2 H), 7.34 (dd, $J$=9.22, 2.05 Hz, 1 H), 7.55 (d, $J$=1.79 Hz, 1 H), 7.65 (d, $J$=8.45 Hz, 2 H), 7.91 (d, $J$=8.96 Hz, 1 H), 8.00 (d, $J$=8.45 Hz, 2 H); MS (ESI) $(M+H)^+$ 485.0.

**Example 12**

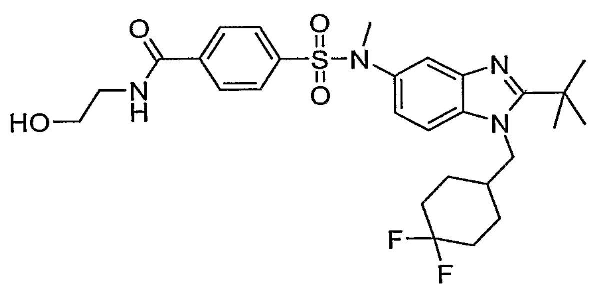
**4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-hydroxy-*N*-methylbenzamide**



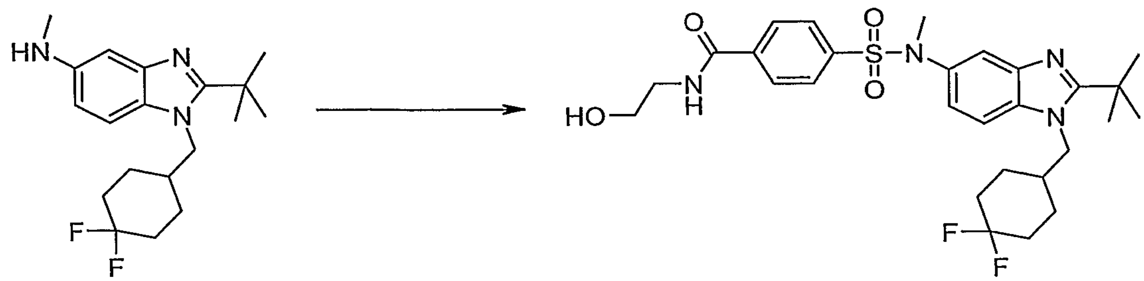
2-*tert*-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (60 mg, 0.199 mmol) and 4-chlorosulfonyl benzoic acid (57 mg, 0.259 mmol) were stirred in 5 mL of DMF containing DIPEA (0.052 mL, 0.299 mmol) at rt for 3h. N-Methyldroxylamine hydrochloride (25 mg, 0.299 mmol), HATU (83 mg, 0.219 mmol) and DIPEA (0.175 mL, 0.995 mmol) were added and the solution was stirred at rt for 3h. The solvent was evaporated. The product was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% $CH_3CN/H_2O$ and lyophilized affording the title compound as the corresponding TFA salt. Yield: 6 mg (6%). $^1$H NMR (600 MHz, $CD_3OD$) δ 1.52 - 1.55 (m, 2 H), 1.57 - 1.63 (m, 2 H), 1.68 (s, 9 H), 2.33 - 2.39 (m, 1 H), 3.29 - 3.30 (m, 3 H), 3.33 - 3.38 (m, 5 H), 3.93 (d, *J*=3.33 Hz, 1 H), 3.95 (d, *J*=3.07 Hz, 1 H), 4.53 (d, *J*=7.42 Hz, 2 H), 7.32 (dd, *J*=8.96, 2.05 Hz, 1 H), 7.55 (d, *J*=1.79 Hz, 1 H), 7.59 (d, *J*=7.68 Hz, 2 H), 7.71 - 7.76 (m, 2 H), 7.89 (d, *J*=8.96 Hz, 1 H); MS (ESI) $(M+H)^+$ 515.0.

**Example 13**

**4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-(2-hydroxyethyl)benzamide**

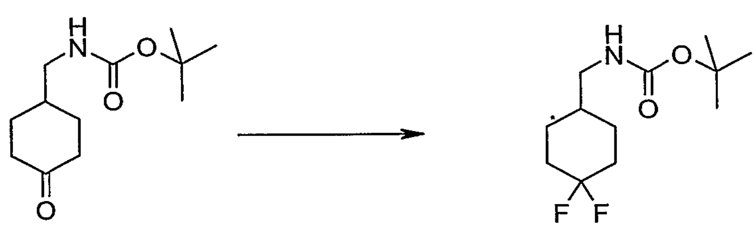


**Step A. 4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-(2-hydroxyethyl)benzamide**



2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-*N*-methyl-1*H*-benzimidazol-5-amine for preparation see following steps B to G) (50 mg, 0.149 mmol) and 4-chlorosulfonyl benzoic acid (43 mg, 0.194 mmol) were stirred in 5 mL of DMF containing DIPEA (0.039 mL, 0.224 mmol) at rt for 3h. Ethanolamine (0.012 mL, 0.194 mmol), HATU (62 mg, 0.223 mmol) and DIPEA (0.130 mL, 0.745 mmol) were added and the solution was stirred at rt for 3h. The solvent was evaporated. The product was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% $CH_3CN/H_2O$ and lyophilized affording the title compound as the corresponding TFA salt. Yield: 14 mg (14%). $^1H$ NMR (600 MHz, $CD_3OD$) δ 1.52 - 1.61 (m, 2 H), 1.67 (s, 9 H), 1.71 - 1.81 (m, 4 H), 2.04 - 2.11 (m, 2 H), 2.21 - 2.27 (m, 1 H), 3.30 (s, 3 H), 3.51 (t, *J*=5.50 Hz, 2 H), 3.71 (t, *J*=5.63 Hz, 2 H), 4.54 (d, *J*=7.42 Hz, 2 H), 7.31 (d, *J*=8.96 Hz, 1 H), 7.53 (s, 1 H), 7.63 (d, *J*=7.42 Hz, 2 H), 7.86 (d, *J*=8.96 Hz, 1 H), 7.95 (d, *J*=7.42 Hz, 2 H); MS (ESI) $(M+H)^+$ 563.0; Anal. Calcd(%) for $C_{28}H_{36}N_4O_4SF_2$ + 1.5 TFA + 0.8 $H_2O$: C, 49.77; H, 5.27; N, 7.49. Found: C, 49.77; H, 5.27; N, 7.43.

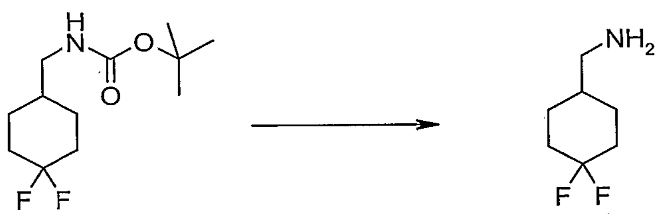
**Step B. *tert*-Butyl [(4,4-difluorocyclohexyl)methyl]carbamate**



4-N-Boc-aminomethyl cyclohexanone (1.00g, 4.4 mmol) was dissolved in 30 mL of DCM at 0°C. DAST (1.45 mL, 11.0 mmol) was added dropwise and the solution was stirred at rt overnight. The solution was washed with aqueous 5% $KHSO_4$ solution,

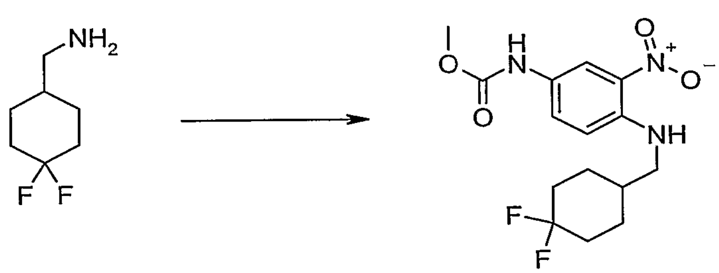
saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using 3:1 / hexanes : EtOAc as eluent. Yield: 508mg (46%). $^1$H NMR (400 MHz, CHLOROFORM-D) δ 1.19 - 1.36 (m, 2 H), 1.44 (s, 9 H), 1.51 - 1.56 (m, 1 H), 1.59 - 1.75 (m, 2 H), 1.75 - 1.84 (m, 2 H), 2.01 - 2.16 (m, 2 H), 3.03 (t, *J*=6.54 Hz, 2 H), 4.62 (br.s, 1 H).

**Step C. [(4,4-Difluorocyclohexyl)methyl]amine hydrochloride**



*tert*-Butyl [(4,4-difluorocyclohexyl)methyl]carbamate (505 mg, 2.03 mmol) was stirred in 5 mL of 1M HCl/AcOH at rt for 2h. The solvent was evaporated. The residue was washed with ether, filtered and dried. Yield: 330 mg (88%). $^1$H NMR (400 MHz, METHANOL-$D_4$) δ 1.28 - 1.40 (m, 2 H), 1.71 - 1.82 (m, 2 H), 1.84 (d, *J*=3.12 Hz, 2 H), 1.86 - 1.89 (m, 1 H), 2.03 - 2.15 (m, 2 H), 2.85 (d, *J*=7.03 Hz, 2 H).

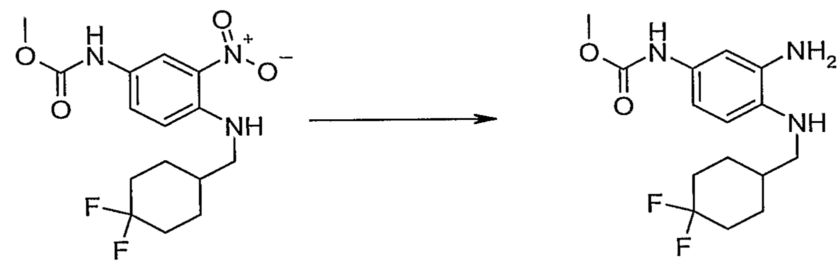
**Step D. Methyl (4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)carbamate**



Following the same procedure as in Step C of Example 1 using [(4,4-difluorocyclohexyl)methyl]amine hydrochloride (210 mg, 1.12 mmol), methyl (4-fluoro-3-nitrophenyl)carbamate (200 mg, 0.934 mmol) and TEA (0.390 mL, 2.80 mmol) in 10 mL of EtOH. The crude product was purified by silica gel flash chromatography using 5% ether/DCM as eluent. Yield: 200 mg (62%). $^1$H NMR (400 MHz, CHLOROFORM-D) δ 1.34 - 1.47 (m, 2 H), 1.65 - 1.75 (m, 2 H), 1.78 -

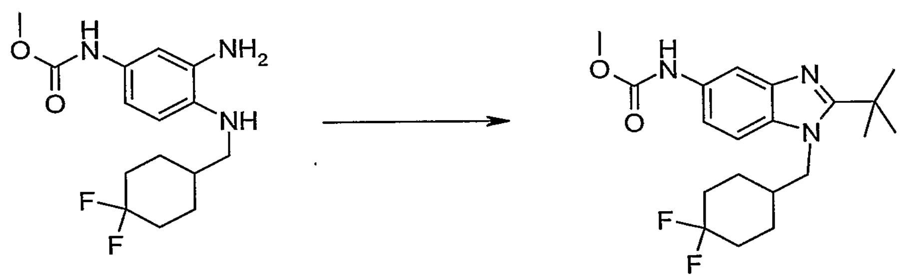
1.85 (m, 1 H), 1.90 - 1.93 (m, 1 H), 1.94 - 1.97 (m, 1 H), 2.10 - 2.21 (m, 2 H), 3.23 (dd, *J*=6.64, 5.66 Hz, 2 H), 3.78 (s, 3 H), 6.48 (br.s, 1 H), 6.83 (d, *J*=9.18 Hz, 1 H), 7.66 (br.s, 1 H), 8.05 (br.s, 1 H), 8.07 (d, *J*=2.54 Hz, 1 H).

**Step E. Methyl (3-amino-4-{[(4,4-difluorocyclohexyl)methyl]amino}phenyl)carbamate**



Following the same procedure as in Step D of Example 1 using methyl (4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)carbamate (200 mg, 0.583 mmol) and a catalytic amount of 10% Pd/C in 20 mL of EtOAc. Yield: 185 mg (99%). MS (ESI) $(M+H)^+$ 314.29.

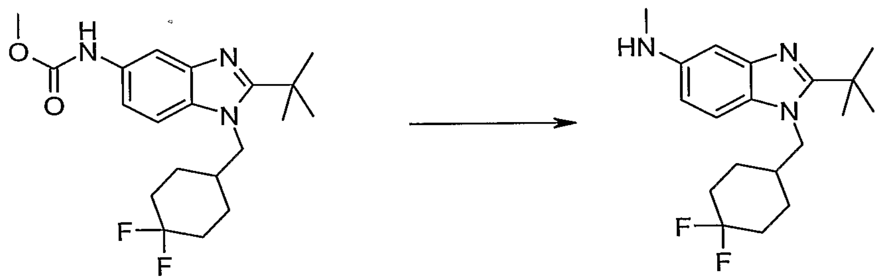
**Step F. Methyl {2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}carbamate**



Methyl (3-amino-4-{[(4,4-difluorocyclohexyl)methyl]amino}phenyl)carbamate (185 mg, 0.590 mmol) and DMAP (15 mg, 0.118 mmol) were dissolved in 10 mL of DCM. Trimethylacetyl chloride (0.080 mL, 0.649 mmol) was added dropwise and the solution was stirred at rt for 2h. The solution was washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was concentrated. The residue was dissolved in 4 mL of DCE and $P_2O_5$ (catalytic) was added and the

solution was heated at 125°C for 1h using a Personal Chemistry microwave apparatus. The solution was washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using 50 to 75% EtOAc / hexanes. Yield: 122 mg (54%); $^1$H NMR (400 MHz, CHLOROFORM-D) δ 1.43 - 1.52 (m, 2 H), 1.55 (s, 9 H), 1.57 - 1.66 (m, 2 H), 1.67 - 1.74 (m, 2 H), 2.08 - 2.18 (m, 3 H), 3.79 (s, 3 H), 4.19 (d, *J*=7.42 Hz, 2 H), 6.63 (br.s, 1 H), 7.23 (d, *J*=8.79 Hz, 1 H), 7.37 - 7.46 (m, 1 H), 7.62 (d, *J*=1.76 Hz, 1 H).

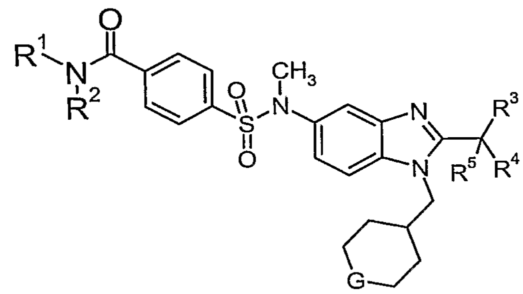
**Step G. 2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-*N*-methyl-1*H*-benzimidazol-5-amine**



Methyl {2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}carbamate (115 mg, 0.303 mmol) was dissolved in 10 mL of THF at 0°C. 1M HCl/ether (0.425 mL, 0.424 mmol) was added and the solution was stirred at 0°C for 15 min. $LiAlH_4$ (57 mg, 1.52 mmol) was added slowly and the solution was stirred at rt overnight. The reaction was quenched at 0°C by the addition of MeOH (1 mL) and water (2 mL). Anhydrous $Na_2SO_4$ (5.0 g) was added and the solution stirred at rt for 30 min. The solution was filtered and the solvent evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. Yield: 95 mg (93%). $^1$H NMR (400 MHz, CHLOROFORM-D) δ 1.41 - 1.51 (m, 2 H) 1.54 (s, 9 H) 1.57 - 1.67 (m, 2 H) 1.68 - 1.76 (m, 3 H) 2.07 - 2.17 (m, 3 H) 2.87 (s, 3 H) 4.15 (d, *J*=7.42 Hz, 2 H) 6.61 (dd, *J*=8.59, 2.34 Hz, 1 H) 7.01 (d, *J*=1.95 Hz, 1 H) 7.09 (d, *J*=8.59 Hz, 1 H).

What is claimed is:

1. A compound of Formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



**I**

wherein

G is selected from –O- and –$CF_2$-;

$R^1$ and $R^2$ are independently selected from –H, hydroxy, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, and hydroxy-$C_{1-4}$alkyl; and

$R^3$, $R^4$ and $R^5$ are independently selected from fluoro and methyl.

2. A compound as claimed in claim 1, wherein

G is selected from –O- and –$CF_2$-;

$R^1$ and $R^2$ are independently selected from –H, hydroxy, methyl, 2-hydroxylethyl; and

$R^3$, $R^4$ and $R^5$ are independently selected from fluoro and methyl.

3. A compound as claimed in claim 1,

wherein

G is selected from –O- and –$CF_2$-;

$R^1$ and $R^2$ are independently selected from –H, hydroxy, methyl, 2-hydroxylethyl; and

$R^3$, $R^4$ and $R^5$ are methyl.

4. A compound as claimed in claim 1, wherein

G is –O-;

$R^1$ and $R^2$ are independently selected from –H, hydroxy, methyl, 2-hydroxylethyl with $R^1$ and $R^2$ being different groups; and

$R^3$, $R^4$ and $R^5$ are methyl.

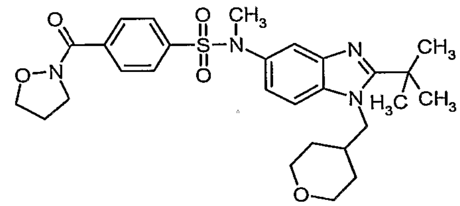
5. A compound as claimed in claim 1, wherein

G is $-CF_2-$;

$R^1$ and $R^2$ are independently selected from –H, hydroxy, methyl, 2-hydroxylethyl with $R^1$ and $R^2$ being different groups; and

$R^3$, $R^4$ and $R^5$ are methyl.

6. A compound selected from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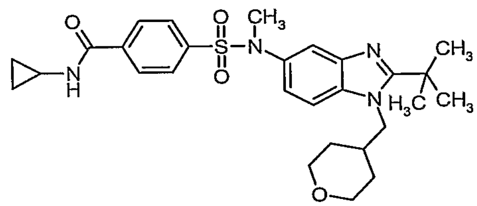
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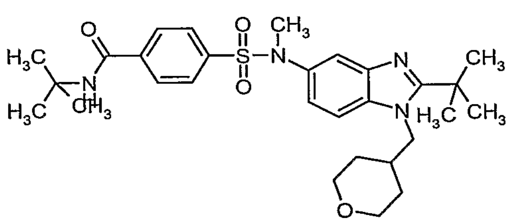
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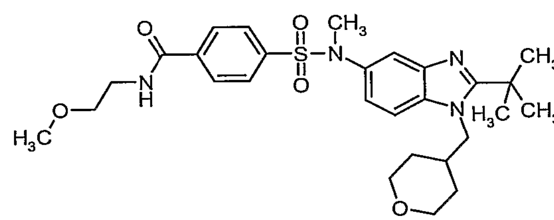
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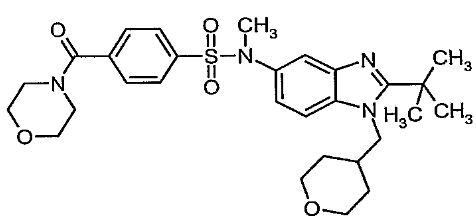
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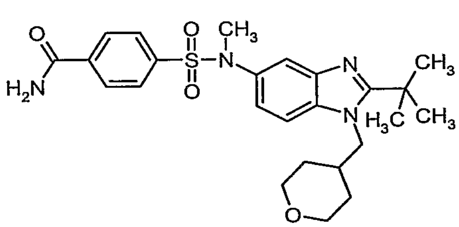
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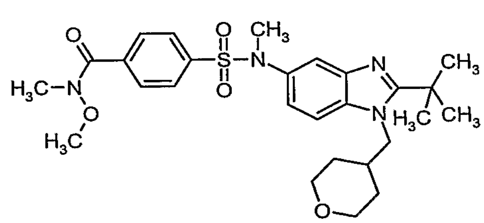
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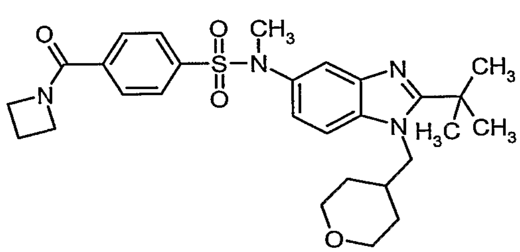
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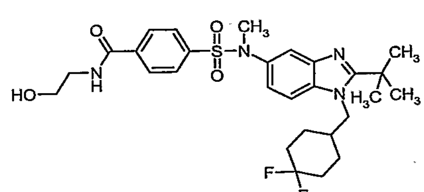
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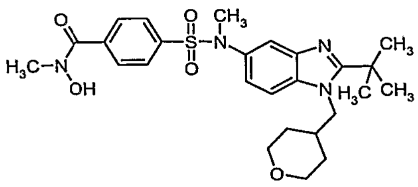
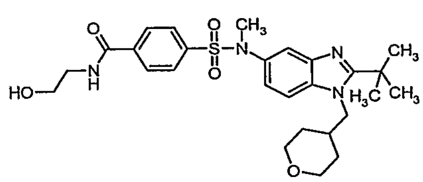
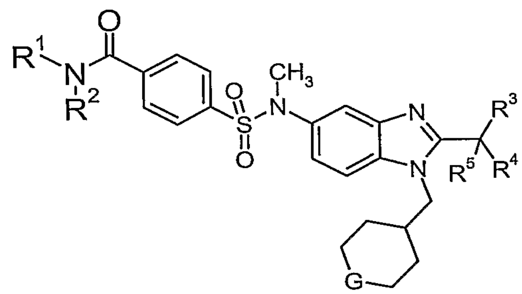


, and

pharmaceutically acceptable salts thereof.

7. A compound of Formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



I

wherein

G is selected from –O-, -CHF-, and –$CF_2$-;

$R^1$ and $R^2$ are independently selected from –H, hydroxy, $C_{1-4}$alkyl, $C_{3-6}$cycloalkyl, $C_{1-4}$alkoxy-$C_{1-4}$alkyl, $C_{1-4}$alkoxy, and hydroxy-$C_{1-4}$alkyl; or $R^1$ and $R^2$ together with the nitrogen linked thereto form a $C_{2-5}$cycloheteroalkyl; and

$R^3$, $R^4$ and $R^5$ are independently selected from fluoro and methyl.

8. A compound according to any one of claims 1-7 for use as a medicament.

9. The use of a compound according to any one of claims 1-7 in the manufacture of a medicament for the therapy of pain.

10. The use of a compound according to any one of claims 1-7 in the manufacture of a medicament for the treatment of anxiety disorders.

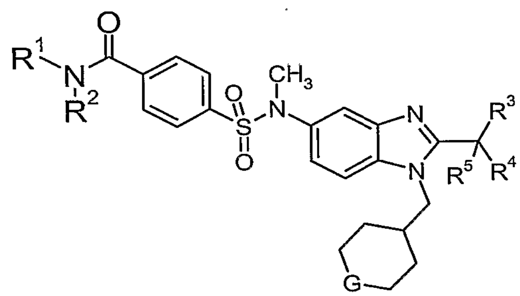
11. The use of a compound according to any one of claims 1-7 in the manufacture of a medicament for the treatment of cancer, multiple sclerosis, Parkinson's disease,

Huntington's chorea, Alzheimer's disease, gastrointestinal disorders and cardiovascular disorders.

12. A pharmaceutical composition comprising a compound according to any one of claims 1-7 and a pharmaceutically acceptable carrier.

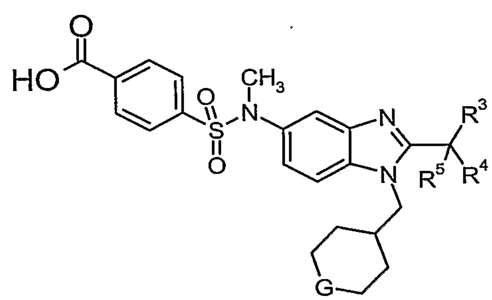
13. A method for the therapy of pain in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-7.

14. A method for preparing a compound of Formula I, comprising:



**I**

reacting a compound of Formula II with $HNR^1R^2$,



**II**

wherein

G is selected from –O-, -CHF-, and –$CF_2$-;

$R^1$ and $R^2$ are independently selected from –H, hydroxy, $C_{1\text{-}4}$alkyl, $C_{3\text{-}6}$cycloalkyl, $C_{1\text{-}4}$alkoxy-$C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkoxy, and hydroxy-$C_{1\text{-}4}$alkyl; or $R^1$ and $R^2$ together with the nitrogen linked thereto form a $C_{2\text{-}5}$cycloheteroalkyl; and

$R^3$, $R^4$ and $R^5$ are independently selected from fluoro and methyl.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2005/001400

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC: see extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,A | WO 2004108712 A1 (ASTRAZENECA AB), 16 December 2004 (16.12.2004) -- | 1-14 |
| A | WO 02085866 A1 (ASTRAZENECA AB), 31 October 2002 (31.10.2002) -- -------- | 1-14 |

☐ Further documents are listed in the continuation of Box C.  ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 24 November 2005 | 01-12-2005 |
| Name and mailing address of the ISA/<br>Swedish Patent Office<br>Box 5055, S-102 42 STOCKHOLM<br>Facsimile No. +46 8 666 02 86 | Authorized officer<br>Renzo Verboom/ELY<br>Telephone No. +46 8 782 25 00 |

Continuation of second sheet

***C07D 405/06*** (2006.01)
***A61K 31/4184*** (2006.01)
***A61K 31/422*** (2006.01)
***A61K 31/5377*** (2006.01)
***A61P 1/00*** (2006.01)
***A61P 25/00*** (2006.01)
***A61P 25/16*** (2006.01)
***A61P 25/22*** (2006.01)
***A61P 25/28*** (2006.01)
***A61P 35/00*** (2006.01)
***A61P 9/00*** (2006.01)
***C07D 235/08*** (2006.01)
***C07D 405/14*** (2006.01)
***C07D 413/14*** (2006.01)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2005/001400

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13
   because they relate to subject matter not required to be searched by this Authority, namely:

   Claim 13 relates to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic

   .../...

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Box II.1

methods /Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| WO | 2004108712 | A1 | 16/12/2004 | AU | 2003280905 | A | 00/00/0000 |
| | | | | EP | 1579119 | A | 28/09/2005 |
| | | | | SE | 0301701 | D | 00/00/0000 |
| WO | 02085866 | A1 | 31/10/2002 | AU | 7477201 | A | 14/01/2002 |
| | | | | BG | 108271 | A | 30/12/2004 |
| | | | | CA | 2414995 | A | 10/01/2002 |
| | | | | CA | 2444381 | A | 31/10/2002 |
| | | | | CN | 1503787 | A | 09/06/2004 |
| | | | | CZ | 20032833 | A | 12/05/2004 |
| | | | | EE | 200300524 | A | 16/02/2004 |
| | | | | EP | 1307481 | A | 07/05/2003 |
| | | | | EP | 1390350 | A | 25/02/2004 |
| | | | | HU | 0303825 | A | 01/03/2004 |
| | | | | IL | 158142 | D | 00/00/0000 |
| | | | | JP | 2004502416 | T | 29/01/2004 |
| | | | | JP | 2004528334 | T | 16/09/2004 |
| | | | | MX | PA03009558 | A | 12/02/2004 |
| | | | | NO | 20034665 | A | 10/12/2003 |
| | | | | NZ | 528403 | A | 27/05/2005 |
| | | | | PL | 366517 | A | 07/02/2005 |
| | | | | SE | 0101387 | D | 00/00/0000 |
| | | | | SK | 13032003 | A | 03/01/2005 |
| | | | | US | 20040116465 | A | 17/06/2004 |
| | | | | ZA | 200307752 | A | 03/01/2005 |